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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 09.01.2001
Applicant's or agent's file reference HMJ02856WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03189	23/09/1999	23/09/1998

Applicant
SCHOOL OF PHARMACY, UNIVERSITY OF LONDON et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel.+49 89 2399-8071

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMJ02856WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03189	23/09/1999	23/09/1998
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant SCHOOL OF PHARMACY, UNIVERSITY OF LONDON et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/2000	09.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baumgärtner, H Telephone No. +49 89 2399 8480

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03189

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-29 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Drawings, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12, 16-23
	No:	Claims	13-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-20, 22-23 for claim 21 s. separate sheet
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents which are referred to in this communication are numbered in the order of their listing in the International Search Report.

D1: WO 94 02506 A (GIBBONS WILLIAM ANTHONY ;TOTH ISTVAN (GB); UNIV LONDON PHARMACY (G) 3 February 1994 cited in the application **relates to peptide compounds** (p.1/1st para) which comprise a **lipophilic anchor section** formed from at least one **fatty amino acid moiety** (cf. p.5/l.9 - formula I and p.5/l.17 C6-24 alkyl...) **joined to the central amino acid** of the **matrix core section** comprising n levels of **dendritically linked trifunctional amino acid moieties** (cf. p.1/l.5-8; p.6/l.19-20) via a **peptide bond** (p.7/l.27-30). The **amino acid unit** on which a dendritic structure **is** based is preferably **lysine** (p.7/l.4-5). A pharmaceutically active compound is formed by joining to each of the terminal functionalities a **pharmaceutically active substituent** (p.8/l.20-24, e.g. peptide antigen p.1/l.8-9), further comprising a **pharmaceutically acceptable carrier** (p.9/l.10 and claim 10/11).

D2: EP-A-0 884 327 (UNIV LONDON PHARMACY) 16 December 1998 **describes polypeptide compounds** which have **n levels** (p.2/l.39) **of dendritically linked units** (**at least two dendrons** extend from a focal group - p.2/l.30-31, the focal group preferably being **lysine or ornithine** - p3/l.15) formed **from amino acids** having reactive groups, e.g. carboxylic acid or amine groups in their side chains (p.2/l.3-5). **To at least 2 of the terminal branches of one of the dendrons** are **attached anchor groups** (p.2/l.5), cf. formula on p.2/l.42 ff. The **terminal branches of the second dendrons** may be **conjugated via** the **terminal -NH-** e.g. **to a group R12, R12 being an active ligand** or an organic group comprising a sugar moiety (p.2/l.56-p.3/l.1 and compare with Fig.1/comp.3a-3c of application).
Cf. particular **compounds 1.1-1.7** of (comparative) example , p.6-8.

D3: CHEMICAL ABSTRACTS, vol. 129, no. 6, 10 August 1998 (1998-08-10) Columbus, Ohio, US; abstract no. 68022, SAKTHIVEL, T. ET AL: ' **Synthesis and physicochemical properties of lipophilic polyamide dendrimers**' XP002098793

D4: KABANOV A V ET AL: 'DNA COMPLEXES WITH POLYCATIONS FOR THE DELIVERY OF GENETIC MATERIALINTO CELLS' BIOCONJUGATE CHEMISTRY, vol. 6, no. 1, 1 January 1995, pages 7-20, XP000494803 cited

D5: WO 98 40502 A (LIFE TECHNOLOGIES INC) 17 September 1998 discloses a **composition for transfecting a cell** which comprises one ore **more nucleic acid molecules**, one ore more **peptide or proteins** (for enhanced transfection - p.9/L.6-30) and one ore more **transfection agents** e.g. dendrimers (claim1, 8 and 15 and p.32/l.11).
According to D5 in general **any dendrimer** that **can be employed to introduce nucleic** acid into any cell, particularly into a eukaryotic cell, is **useful in** the **improved transfection compositions** and methods of the invention in D5 (p.11/l.4 seq.). Dendrimers of generation 5 or higher are preferred (p.11/l.6).
Dendrimers of the D5 invention include those in which the **terminal functional groups at the outer surface of the dendrimer provides a positive charge density**, e.g. as with terminal amine functional groups. [...] Of particular interest are dendrimers that are **functionalised by reaction with cationic amino acids, such as lysine** or arginine (p.11/l.11-17 - cf. also p.37/l.26-28: "...those having cationic amino acids or other cationic species at their outer surface or "SUPERFECT"...").

Novelty(i), Inventive Step(ii) and Industrial Applicability (iii) - Art. 33 (1)-(4)

i.

Claim 1: a **complex** comprising **in admixture**
a cationic polymer compound
and
an anionic active compound
characterised.... that said **polymer compound** comprises
a **dendritic core** having
min. **1 dendron**
- having n levels of dendritically linked trifunctional monomer units
- **cationic groups at min.50%** of the terminal branches of at least 1 dendron
an **anchor moiety**
compr. at least two lipophilic C6-24 alkyl.gr. covalently conjugated in the polymer comp.

is **novel vis-à-vis D1 :**

Though on p.3/l.12-13 it is for instance stated that the **peptide antigen** (i.e. an oligo- or a poly-nucleotide - p.3/l.26-30) is **joined to the four amine functionalities** of the core, i.e. an anionic active compounds could be considered to be implicitly disclosed (the anionic active compound of the application being oligo/poly-nucleotide, resp. RNA or DNA nucleic acids - p. 7/l.14 of the specification) and with the additional information in the application on p.8/l.3 seq. defining the bondages to be counterionically or covalently (which would be also the case in D1), it is acknowledged that claim1 and dependant claims 1-12 are rendered novel by defining **the cationic moieties in terms of a functional feature (min. 50% of cationic groups** on the terminal branches...), whereas in D1 merely a considerable likelihood that at least half of the terminal groups are cationic can be assumed.

For the same reasoning the claims are **novel vis-à-vis D2** (cf. ex. 1/comp. ex. 1 (p.6-8) in comparison with Fig.1 and Fig.3 of the application).

Thus, claims 16 (complex of an oligo- or polynucleotide and an anchored cationic PP) **and 21** are **novel**, too.

Claims 13-14 (complex with pendant amino groups) are **not novel** vis-à-vis **D1**, the latter also disclosing pendant amine groups (p. 8/l.14 - "...amine groups as terminal functionalities ....") the anchor group comprising at least two amino acid moieties, each of formula I (p.5/l.8-18 and cf. fig.1).
Claim 15 lacks novelty, too, as the peptide antigens for instance disclosed in D1 are indeed oligo- or polynucleotide and thus fall withing the definition of claim 13.

ii.
The problem underlying claims 1, 16 and 21 is to provide a further complex for an improved transfection of oligo/poly-nucleotides (pref. single- or double stranded linear or circular DNA -cf. claim 2). The solution given consists of a complex as described in claim 1 (s. above).
It is, however, considered to have been obvious to think of the solution when considering the teaching of D1, where similar dendrimers have been described in combination with the teaching of D5 where the aspect of using cationic dendrimers had already been considered and shown to lead to improved transfection properties.
Thus, **claims 1-12 and 16-21** are considered **not** to be **inventive.**

The in vitro method of **claims 22 and 23** appears to **have been obvious** to the skilled person when considering the teaching D5 where e.g. dendrimers are described as known transfection enhancers and e.g. ex. 3/p.53 describes an in-vitro method for testing transfection enhancement.

iii.
For the assessment of the present **claim 21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.